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Review

Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness

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The panoply of cognitive, affective, motivational, and social functions that underpin everyday human experience requires precisely choreographed patterns of interaction between networked brain regions. Perhaps not surprisingly, diverse forms of psychopathology are characterized by breakdowns in these interregional relationships. Here, we discuss how functional brain imaging has provided insights into the nature of brain dysconnectivity in mental illness. Synthesizing work to date, we propose that genetic and environmental risk factors impinge upon systems-level circuits for several core dimensions of cognition, producing transdiagnostic symptoms. We argue that risk-associated disruption of these circuits mediates susceptibility to broad domains of psychopathology rather than discrete disorders.

Introduction

The human brain comprises some 100 billion neurons and possesses a computational capacity that far exceeds even the most powerful computers. This impressive degree of cerebral horsepower is not the product of some 10^{11} automatons working in isolation. Rather, the massive and massively flexible capacity of the human mind is enabled by the ability of these neurons to organize themselves into coherent coalitions, dynamically arranged in precise temporal and spatial patterns. The number of neurons in the human brain is dwarfed only by the number of their potential connections: even if only two-way interactions are considered they exceed nearly 100 trillion, if one accepts a count of synapses as proxy. Simply put, what makes a brain a brain is its ability to flexibly create, adapt, and disconnect networks in a manner that permits efficient communication within and between populations of neurons, a feature that we call connectivity. The panoply of cognitive, affective, motivational, and social processes that underpin normative human experience requires precisely choreographed interactions between networked brain regions. Aberrant connectivity patterns are evident across all major mental disorders, suggesting that breakdowns in this interregional choreography lead to diverse forms of psychological dysfunction.

The purpose of this review is three-fold. First, we will evaluate current conceptual and methodological approaches to measuring neural connectivity using functional brain imaging. Second, we will argue that connectivity analysis can inform ongoing debates about the classification of mental illness. We will demonstrate that transdiagnostic patterns of dysconnectivity underlie transdiagnostic patterns of psychiatric symptoms, and may explain why comorbidity among diagnostic categories is so frequently observed. Third, we will propose that genetic and environmental risk factors for mental illness induce susceptibility to broad domains of psychopathology, rather than discrete categorical disorders, because they disrupt core connectivity circuits in ways that necessarily produce transdiagnostic symptoms (Figure 1; Figure 2). To illustrate this point, we will show that several genetic variants that induce broad susceptibility to mental illness perturb specific connectivity circuits to engender disorder-spanning symptoms.

Connectivity as Functional Integration

Brain information processing can be conceptualized along two organizational principles: functional segregation and functional integration (Friston, 1994). Functional segregation refers to specialized processing that takes place in "local" populations of neurons, often defined by common functional properties (for example, language processing in neurons in the left inferior frontal gyrus). Such specialization extends even beyond the processing of stimulus categories or external stimulus features to encompass motivationally salient contextual elements of a stimulus, for example neuronal encoding of internal goal representations in the dorsolateral prefrontal cortex (Miller and Cohen, 2001). However, successful execution of even simple behaviors requires that the specialized outputs of each of these functionally segregated neuronal populations be integrated. Connectivity makes this functional integration possible. The anatomical framework underlying connectivity has been the subject of several excellent recent reviews (Johansen-Berg and Rushworth, 2009; Sporns, 2011). Here, we focus on the functional mechanisms that permit integration between specialized processing nodes.

Connectivity mediates the convergence of manifold computations about external sensory stimuli and internal states, and serves a vital enabling function through which such computations are ultimately able to influence behavior. Patterns of connectivity across regions are dynamically arranged according

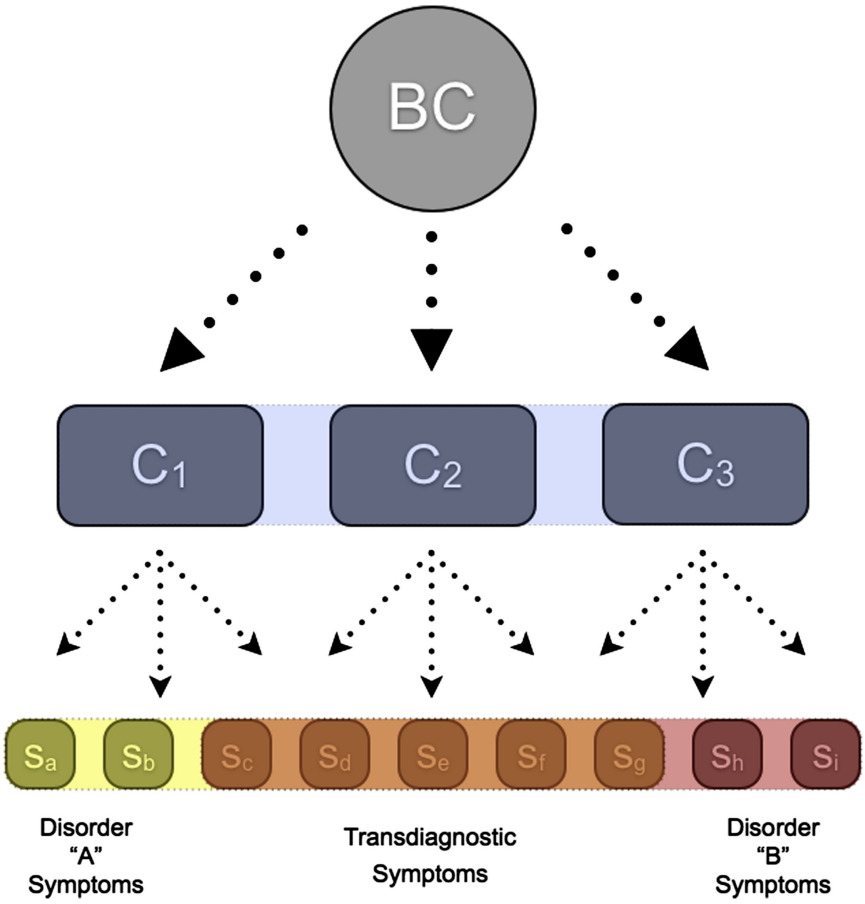

Figure 1. Overview of the Model: Common Symptoms Arise from Common Circuit Dysfunction

A pleiotropic risk factor for psychopathology increases susceptibility to disorders "A" and "B." This factor alters the function of brain circuit "BC" that supports multiple related cognitive processes (C1–C3, comprising a "domain" of cognition; blue shading). Deficits in these cognitive processes lead to symptoms Sa-Si that are lawfully related to the specific cognitive domain, but which overlap diagnostic taxons. Some of these symptoms will constitute diagnostic criteria for categorical disorder "A" but not disorder "B" (yellow shading), and some symptoms will be relatively selective for disorder "B" but not disorder "A" (red shading). However, the plurality of symptoms will overlap the two diagnostic categories ("transdiagnostic symptoms," orange shading). This highlights the idea that connectivity circuits convey cognitive and symptom domain-specific, but disorder-general, genetic risk for mental illness.

to moment-to-moment changes in the array of available external sensory inputs, internal states, and response options. The complexity inherent in this constant adaptive reconfiguration of functional integration between regions would appear to provide many opportunities for failure, each accompanied by a characteristic set of cognitive, emotional, motivational and social consequences, or symptoms.

It has long been noted that alterations in circuit-level connectivity can have a more pronounced impact on behavior and psychopathology compared to disruptions in regional activity alone. The notion that major forms of mental illness, such as schizophrenia, are essentially disorders of dysconnectivity has a long history that stretches back more than a century. Such "disconnection hypotheses" motivated some of the earliest neuroimaging analyses of connectivity and set the stage for the thousands of connectivity studies in health and disease that have been reported since. These investigations have significantly advanced our understanding of both the functional underpinnings of normative cognition and the pathophysiology of mental illness. These advances are due in large part to the development of multiple complementary methods for measuring functional integration.

Approaches to Connectivity Measurement

Connectivity approaches based on the measurement of brain function can be subdivided on the basis of whether they assess interregional statistical dependencies in signal (functional connectivity) or whether they estimate causal interactions between regions (effective connectivity). In both cases, connectivity measures are obtained by analyzing changes in functional MRI blood oxygen level-dependent (BOLD) signal across multiple sequential measurements in two or more brain regions. If BOLD signal acquisition takes place at rest, these measures will reflect intrinsically organized patterns of spontaneous signal fluctuation, termed "resting-state connectivity." If acquisition takes place during the performance of a cognitive task, these measures will reflect the dynamic organization of systems-level networks that are arranged according to the specific cognitive demands of the task (task-based connectivity).

Functional Connectivity

Functional connectivity metrics quantify linear statistical dependencies between BOLD signal time series in two or more brain regions. Univariate functional connectivity approaches typically consider correlations between BOLD signal time-course within a "seed" region (defined on a-priori on the basis of anatomy or task-related activity) and BOLD time course in a "target" region. In addition, correlations with seed region BOLD signal can be computed for each voxel across the brain. By appropriately thresholding the resulting whole-brain, voxelwise correlation maps, it is possible to discover networks of regions with patterns of significantly correlated activity. Multivariate techniques, such as independent component analysis (ICA) (Calhoun et al., 2004), principal component analysis (Metzak et al., 2011), and partial least-squares (Krishnan et al., 2011) have also been to applied to imaging data sets to assess functional connectivity. These techniques produce maps of spatiotemporal covariance that do not rely on the specification of a-priori seed regions, and can be particularly useful for network discovery or for

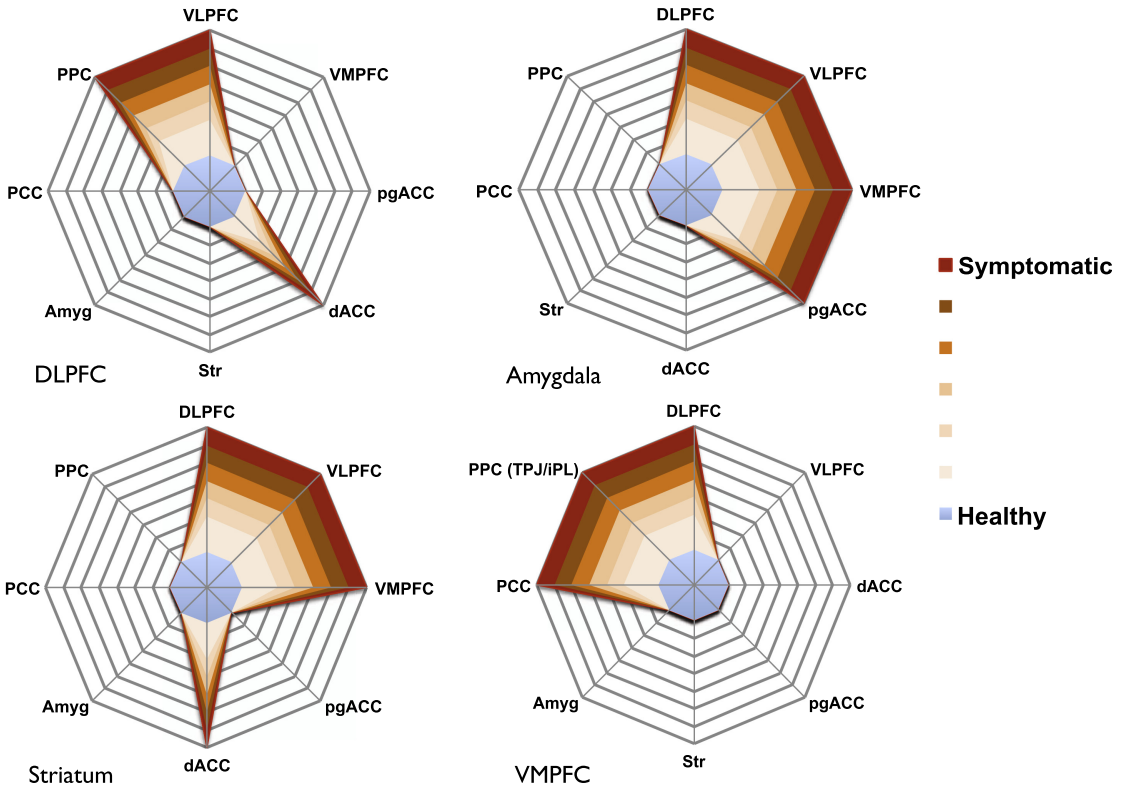

Figure 2. Variability in Circuit-Level Connectivity Leads to Variability in Network-Specific Symptom Expression
Idealized radar plots depict connectivity within four core networks for executive, affective, motivational, and social cognition, centered on DLPFC, amygdala, striatum, and VMPFC, respectively. Distance of each spoke from the center represents the magnitude of deviation in node-wise connectivity from "normal." Functional connectivity is considered here as a normally distributed quantitative trait; thus, "normal" can be thought of as the population mean. Units are arbitrary. Continuous variation in the function of these circuits leads to variability in expression of symptoms linked to each network, ranging from "healthy" (unlikely to cause psychological dysfunction) to "symptomatic" (associated with significant dysfunction, impairment, or distress).

corroborating results produced by seed-based approaches. Both univariate and multivariate techniques can be employed to study resting-state and task-based connectivity.

Resting State Functional Connectivity

Analyses of resting-state functional connectivity (rs-fcMRI) are grounded in the observation that correlated spontaneous low-frequency (<0.1 Hz) fluctuations in BOLD signal are found between numerous and diverse gray-matter processing nodes during rest (Raichle, 2010). Multiple functional networks have been identified, each characterized by coherent patterns of intrinsic activity between nodes. Examples include the "default" mode network, a motor network, a medial lobe memory network, a dorsal attention network, and a frontoparietal control network (Buckner et al., 2008; Van Dijk et al., 2010). Segregated connectivity networks involving the cingulate, hippocampus, striatum, and cerebellum have also been discovered through the use of seed regions (Van Dijk et al., 2010). Of note, the organization of many resting state networks bears close resemblance to patterns of activity observed during task states, suggesting an involvement in aspects of cognition (Smith et al., 2009). Univariate, seed-based techniques are most commonly used to identify rs-fcMRI networks, with seeds often derived from the anatomical parcellation of participants' structural MRIs, functional ROIs based on participant responses to a task, or ROIs defined by previously published functional activation peaks (e.g., from meta-analyses of task data). Multivariate techniques such as ICA largely recapitulate the results from seed-based approaches (Van Dijk et al., 2010). However, ICA can group univariate results differentially across components based on how they interrelate, and may be able to identify networks nodes that are not apparent using univariate methods (Jafri et al., 2008).

Task-Based Functional Connectivity

It is also useful to understand how brain networks adapt and reconfigure themselves in response to an external stimulus or a change in psychological state. Measures of task-based functional connectivity can be thought of as assessing the change in BOLD signal covariance between two or more regions caused by an experimental manipulation. As with rs-fcMRI, both univariate and multivariate techniques can be applied to task data. Univariate approaches typically involve comparing correlation strengths between a seed ROI and a target or set of targets (such as all voxels in the brain) between two experimental conditions. Methods have been developed to allow for functional connectivity assessment in both block-design and event-related fMRI designs, permitting fine-grained evaluation of connectivity changes during discrete stages of cognitive tasks (Rissman et al., 2004). Of the available methods, psychophysical interaction analysis (PPI) has arguably gained the strongest

foothold in the imaging community, owing largely to its relatively straightforward implementation (O'Reilly et al., 2012). In PPI modeling, a seed region is specified, and regression slopes are estimated between activity in that seed and a set of targets. Changes in slopes are calculated on a voxelwise basis between experimental conditions, revealing a map of regions where the influence of seed region activity on target activity is significantly modulated by the experimental manipulation.

Functional connectivity approaches are highly valuable for network discovery. Further, specific functional connectivity network parameters show heritability and are associated with familial risk for psychopathology, suggesting genetic control over inter-regional synchronization (Rasetti et al., 2009; Woodward et al., 2009; Glahn et al., 2010; Repovs et al., 2011). However, it should also be noted that functional connectivity analyses are limited by their model-free, inherently correlational nature. They do not permit directional (i.e., causal) inferences, nor is it possible to discern whether an observed functional relationship between two regions is direct or mediated (Buckholtz et al., 2008).

Effective Connectivity

In contrast to model-free functional connectivity techniques, effective connectivity methods take a hypothesis-driven approach to assessing regional interactivity. Effective connectivity models are explicitly causal. They specify a priori the direction of influence between two or more regions, and the manner by which such causal influences are moderated by specific psychological contexts. A variety of methods have been developed to assess effective connectivity, including dynamic causal modeling (Friston et al., 2003; Krishnan et al., 2011), Granger causality mapping (Roebroeck et al., 2005), multivariate autoregressive modeling (Harrison et al., 2003), graphical causal modeling (Ramsey et al., 2010), and structural equation modeling/path analysis (Mcintosh, 2011). However, the directionality of a putative casual inference is assumed based on one's explicit model, which should be informed by relevant directionally-specific anatomical data. It cannot be measured directly. In other words, the inferential power of effective connectivity is constrained by the validity of the underlying model, which must be examined critically. Thus, it is often useful to empirically confirm causality via complimentary methods, and to test for the best fit among a variety of alternative models.

Imaging the Connectome

A rapidly advancing research frontier uses graph theoretical metrics (Bollobas, 1985) to quantify global properties of all connections between a set of brain regions or nodes, the connectome. These analyses have shown that the topology of the brain connectome is neither completely regular nor fully random, but displays so-called "small world" properties (Bullmore and Bassett, 2011) that are advantageous for efficient information transfer at low wiring costs (Sporns et al., 2005; Achard and Bullmore, 2007; He et al., 2007). Interestingly, the dynamic properties of network activities supported by these empirically observed network topologies suggest that they live on "the edge of chaos," supporting the kind of rapid formation, dissolution and adaptation of connectivity that is critical for mental activity (Bassett et al., 2006). The "hubs" of these networks correspond to the most highly interconnected neural regions, which often map to association cortices (He et al., 2007). A twin study by Fornito and coworkers (2011) showed that 60% of the individual variance in the cost-efficiency metrics of functional circuits is attributable to additive genetic effects (Fornito et al., 2011), suggesting that these methods are potentially useful for understanding neural mechanisms of genetic risk for mental illness (Fornito et al., 2011).

Connectivity and the Classification of Mental Illness

Connectivity analyses in healthy subjects have uncovered specific network mechanisms that underlie diverse aspects of cognitive, affective, motivational, and social functioning. The study of psychopathology has also benefited greatly from this approach. Network disruptions have been found in numerous mental disorders, providing new insights into the pathobiology of mental illness. Additionally, by showing how causal (e.g., genetic) factors for psychopathology disrupt typical patterns of functional integration within distributed brain circuitry, connectivity measurement is emerging as an important tool for discovering etiopathophysiological mechanisms. The picture that is starting to emerge from this line of research has significant implications for how we classify mental disorders.

The application of brain connectivity methods to the study of psychiatric risk mechanisms comes at a moment when the classification of mental illness is under intense discussion and debate (Hyman, 2010). Many in the field believe that the notion of discrete, categorical mental disorders, originally articulated by the Research Diagnostic Criteria and reified in the DSM-III and DSM-IV, is so far removed from biological reality that it actually impedes clinically useful scientific discovery. These psychiatric diagnostic systems employ criteria that are derived from clinician observation, patient self-report, and course. Though originally intended to be "merely" reliable operationalizations of clinical phenomena, over time, these categorical classifications came to be treated as though they were natural kinds—inherently meaningful, ontologically (i.e., biologically) valid taxons. This has produced the assumption that each DSM-defined disorder is "real"—a distinct, independent entity with a unique set of causal factors and pathophysiological processes.

However, several observations belie this assumption. Even at the level of clinical symptoms and signs, dimensionality and comorbidity are pervasive (Kessler et al., 2005; Markon, 2010; Krueger and Markon, 2011), suggesting that the categorical model of the DSM provides a poor fit to the latent structure of psychopathology (Krueger and Markon, 2006). Etiological studies largely reaffirm this observation. By and large, genetic risk for psychiatric disorders is pleiotropic, conferring liability to broad dimensions of symptomatically related disorders, such as schizophrenia and bipolar disorder (International Schizophrenia Consortium et al., 2009; Gejman et al., 2011). Moreover, mental illness is generally characterized by polygenic inheritance (Gejman et al., 2011), with multiple small-effect risk alleles producing a continuous distribution of genetic liability. This implies that disorders may be extreme manifestations of normally distributed quantitative traits (Plomin et al., 2009) and provides a challenge to the validity of categorical models of psychiatric illness and risk. On the whole, extant data suggest

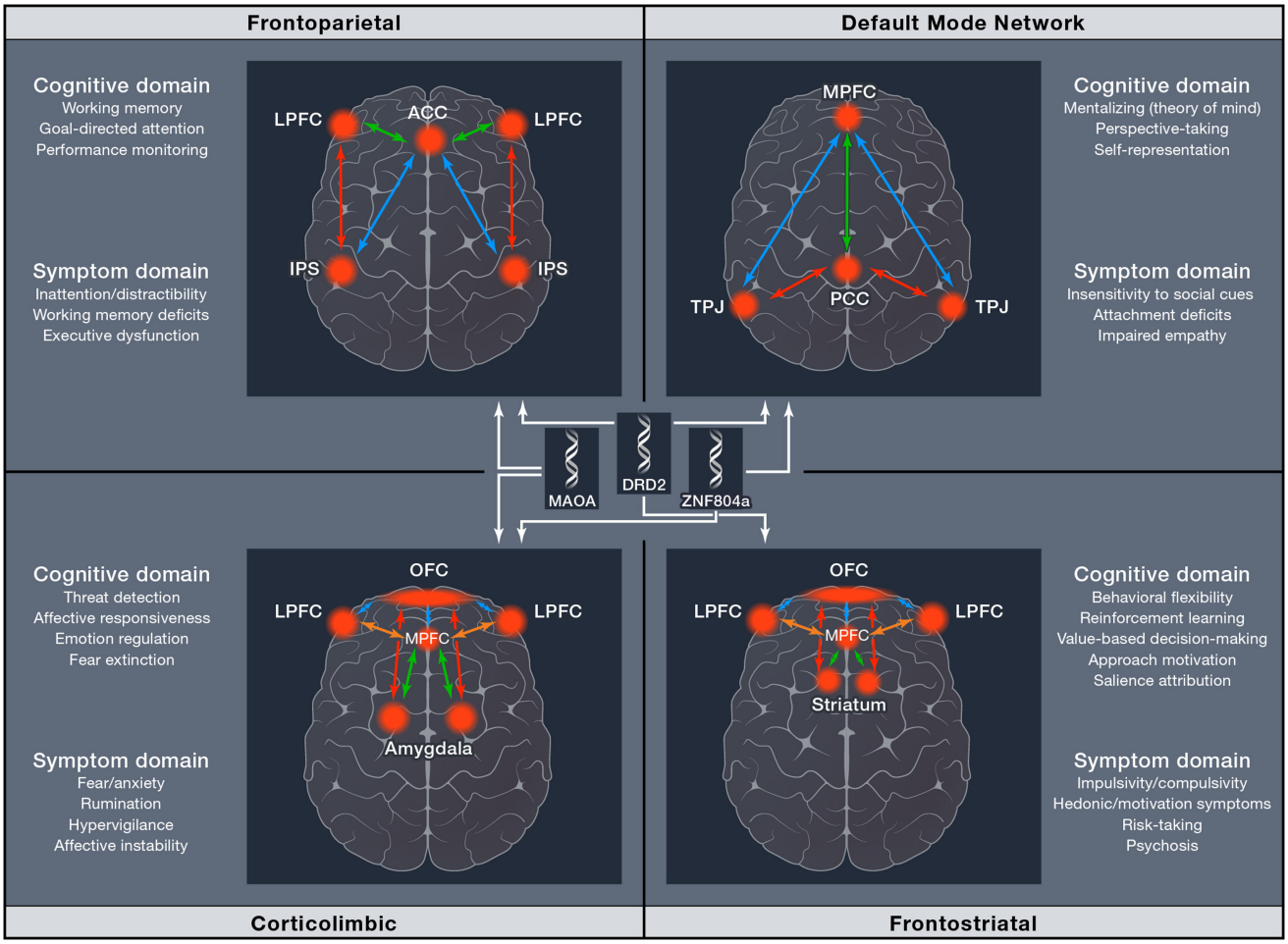

Figure 3. Genetic Variation Affects Risk for Psychopathology by Disrupting Cognition-Specific Brain Circuits
Frontoparietal (LPFC-dACC-IPS), corticolimbic (LPFC-vmPFC/OFC/pgACC-amygdala), frontostriatal (LPFC-vMPFC/OFC-striatum), and DMN (VMPFC-PCC-TPJ/iPL) circuits underpin core executive, affective, motivational, and social domains of cognition, respectively. Heritable variation in the function of these circuits produces deficits in circuit-specific cognitive domains, which manifest as clinical symptoms. Circuit-specific, but transdiagnostic, cognitive processes (cognitive domains) and symptoms (symptom domains) are shown for each network. Allelic variants in MAOA, DRD2, and ZNF804A are shown affecting specific networks that may account for their observed pleiotropic effects, as indicated by available data.

a model of genetic liability to psychopathology that is both continuous and dimensional, involving the graded expression of "symptom domains" that are common to multiple diagnoses rather than specific unique categorical disorders (Figures 1 and 2).

Connectivity data generally support this model. Just as transdiagnostic symptoms overlap comorbid disorders, similar patterns of dysconnectivity are observed across multiple diagnostic boundaries. This atypical connectivity occurs within brain networks that underpin particular domains of cognition (e.g., executive, affective, motivational, and social; Figures 2 and 3). We propose that the network-specific alterations in cognition that arise as a consequence produce network-specific clusters of transdiagnostic symptoms. Accordingly, pleiotropic risk genes appear to increase susceptibility to multiple categorically distinct disorders because they dysregulate connectivity within these networks, altering cognition in a network-specific fashion to bias the expression of disorder-spanning symptoms (Figures 1 and 3). These heritable symptom-specific/disease-general network alterations may reflect an intrinsically meaningful classification of illness, "carving nature at the joints" in a way that DSM diagnostic criteria do not.

This proposal is synergistic with current efforts to redefine psychiatric nosology in terms of underlying biology, such as the Research Domain Criteria (RDoC) initiative of NIMH (Insel et al., 2010). RDoC is organized around domains largely corresponding to neuropsychological functions. What we outline here goes one step further by proposing that specific circuits are biologically meaningful systems-level units of inquiry both for investigating etiology, and for understanding transdiagnostic contributions to psychopathology. In the following section, we will illustrate this concept by showing that DSM-defined categories have diagnostically overlapping patterns of disrupted connectivity within brain circuits implicated in diagnostically overlapping symptom domains. While we use neuropsychological function as an organizing principle in this review, it is

important to note that we do not claim or imply a one-on-one mapping of connectivity abnormalities to cognition. Neural circuit abnormalities, especially if extensive, may map on several cognitive domains as they map on several psychiatric diagnoses. Nevertheless, a useful and somewhat distinct taxonomy of connectivity abnormalities emerges that supports a dimensional view of the symptom architecture underlying psychiatric disease.

Connectivity in Psychopathology: Symptom-Specific Associations to Circuits

Brain Networks for Attention and Cognitive Control

Executive cognition encompasses a suite of cognitive processes that permit the selection and stable maintenance of environmental inputs, and the dynamic control of motor outputs, according internal goals or rules (Miller and Cohen, 2001). Connectivity between lateral frontal, dorsal cingulate, and dorsal parietal cortices appears to be critical for many components of executive cognition, as it is consistently observed during tasks that index working memory, goal-directed attention, conflict detection, and online performance monitoring (Dosenbach et al., 2007; Wang et al., 2010b; Cole and Schneider, 2007; Stevens et al., 2009; Hampson et al., 2006). Deficits in executive cognition comprise a symptom domain that spans a number of disorders, including schizophrenia, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), and substance abuse (Barkley, 1997; Garavan and Hester, 2007; Barch and Smith, 2008; Luck and Gold, 2008; Murrough et al., 2011). Common patterns of atypical connectivity within a dorsal lateral prefrontal-cingulate-parietal network are apparent across these disorders, and may contribute to symptoms relating to attention, working memory, and cognitive control (Tan et al., 2006; Schlösser et al., 2008; Vasic et al., 2009; Woodward et al., 2009; Castellanos and Proal, 2012; Ma et al., 2010). This is consistent with the idea that the common expression of cognitive symptoms among categorically distinct psychopathologies arises from common network pathology.

Brain Networks for Affective Arousal and Regulation

The amygdala, medial prefrontal cortex (ventromedial and medial orbital aspects, along with perigenual cingulate cortex) and lateral prefrontal cortex comprise a corticolimbic circuit that is important for engendering and regulating vigilance and arousal responses to biologically salient stimuli (Pessoa, 2010; Kim et al., 2011). This circuit is consistently engaged during tasks that evoke negative emotional arousal or require the regulation of negative emotional responses (Zald, 2003), suggesting involvement in aversive affective experiences. Affective symptoms such as anxiety, anger, rumination, and hypervigilance are common to many forms of psychopathology, being especially prominent in mood, anxiety and personality disorders. Similar patterns of corticolimbic circuit dysfunction cut across diagnostic taxons, and may explain the transdiagnostic nature of negative affect symptoms. For example, cingulate-amygdala circuit dysfunction predicts high levels of trait negative affect (Pezawas et al., 2005; Cremers et al., 2010), and is evident in schizophrenia (Rasetti et al., 2009), conduct disorder (Marsh et al., 2008), and substance dependence (Upadhyay et al., 2010) in addition to mood and anxiety disorders (Matthews et al., 2008; Dannlowski et al., 2009; Etkin et al., 2010; Etkin and Schatzberg, 2011; Lui et al., 2011). Of note, cross-diagnostic analyses confirm that cingulate-amygdala dysconnectivity is a source of common affective vulnerability in generalized anxiety disorder and MDD (Etkin and Schatzberg, 2011). Similarly, changes in amygdala coupling with DLPFC and ventromedial cortex are present across mood, anxiety, and personality disorders (Marsh et al., 2008; Etkin et al., 2009; Erk et al., 2010; Ladouceur et al., 2011; Motzkin et al., 2011). vMPFC-amygdala dysfunction may have particular relevance to reactive aggression, anger, and irritability, as alterations in this circuit are associated with higher levels of aggressive traits and behavior (Coccaro et al., 2007; Buckholtz et al., 2008; Buckholtz and Meyer-Lindenberg, 2008; Hoptman et al., 2010). Taken together, connectivity studies suggest that corticolimbic circuit dysfunction may account for symptoms of negative affect that are shared among otherwise categorically distinct disorders.

Brain Networks for Reward and Motivation

Functional interactions between prefrontal cortex and striatum are important for integrating reinforcement signals with current goals to flexibly guide attentional focus and action selection (Wickens et al., 2007; Balleine and O'Doherty, 2010). Disrupting frontostriatal information flow impairs motivational and hedonic responses to rewards, cognitive flexibility, and value-based learning and decision making (Kehagia et al., 2010). Such impairments are widespread among mental disorders and cut across diagnostic boundaries; examples include anhedonia (present in both schizophrenia and mood disorders), impulsivity (present in ADHD, substance abuse, schizophrenia, and personality disorders), and compulsivity (present in OCD and substance abuse). Changes in striatal coupling with DLPFC, VMPFC, and cingulate are observed in many of these disorders (Harrison et al., 2009; Heller et al., 2009; Schlagenhauf et al., 2009; Wang et al., 2009; Hamilton et al., 2011; Hong et al., 2010; Park et al., 2010; Liston et al., 2011). Notably, vMPFC-striatal dyregulation is linked to individual variability in impulsivity (Bjork et al., 2011; Diekhof et al., 2011), suggesting a particular relevance of this circuit for disinhibitory or externalizing psychopathology (Krueger et al., 2005). In sum, dysfunctional frontostriatal connectivity may constitute a common neurobiological origin for transdiagnostic reward, motivation and decision-making symptoms in mental illness.

Default-Mode Network Connectivity and Social Cognition

Spontaneous correlated activity is observed between the tempoparietal junction (TPJ), posterior cingulate cortex (PCC), and VMPFC when the brain is at rest (Raichle et al., 2001). The precise function of this "default mode network" (DMN) is still under active debate (Raichle, 2010). However, some have noted that it bears striking resemblance to a circuit that is engaged when people think about the thoughts, beliefs, emotions, and intentions of others (Buckner et al., 2008), prompting speculation that the DMN is involved in self-representation and social cognition (Schilbach et al., 2008). Social cognitive deficits are another class of symptoms that transcend discrete diagnostic categories, and across disorders they are associated with especially poor clinical outcomes (Brüne and Brüne-Cohrs, 2006). Though more research is needed to better characterize the

connectomics of impaired social cognition in psychopathology, dysfunctional DMN connectivity is a pervasive feature of mental illness. Atypical connectivity within the DMN, and between DMN regions and "task-positive" nodes (e.g., DLPFC and cingulate cortex), is apparent in psychosis, personality disorders, mood disorders, and ADHD (Castellanos et al., 2008; Whitfield-Gabrieli et al., 2009; Sheline et al., 2010; Chai et al., 2011; Cole et al., 2011; Garrett et al., 2011; Holt et al., 2011; Motzkin et al., 2011). If the DMN is important for self-representation and social cognition, as has been suggested, alterations in DMN connectivity may contribute to impaired social functioning in diverse disorders.

Connectivity Circuits Convey Symptom-Specific/Disease-General Risk for Mental Illness

As we mentioned above, comorbidity between mental disorders is the rule rather than the exception, invading nearly all canonical diagnostic boundaries. In fact, covariation among psychiatric diagnoses is so prevalent, and so extensive, that it alone belies the artificial nature of phenomenologically based categorical classification. Findings in both community and clinical samples suggest that while DSM-based models of discrete taxa provide a poor fit to the data, dimensional models characterized by continuous liability to psychopathology fit the data well (Krueger and Markon, 2011; Markon et al., 2011). Latent variable approaches have proven especially useful in moving toward an empirical classification of mental illness ("quantitative nosology"). This class of multivariate techniques approximates the latent structure of psychiatric illness by assessing common and unique symptom variance across disorders. These analyses have identified three core syndrome spectra: internalizing (high negative affect; including anxiety, depressive, phobic, and obsessive-compulsive symptoms), externalizing (behavioral disinhibition; including impulsivity, substance abuse, and antisocial behaviors) and thought disorder (atypical/bizarre cognitions; comprising psychotic, paranoiac, and schizoptypal symptoms) (Kotov et al., 2011; Krueger and Markon, 2006).

Twin studies demonstrate that common genetic factors largely account for the observed syndromic clustering, suggesting a biological basis for coherent patterns of comorbidity derived from factor analysis (Kendler et al., 2003, 2011). Put another way, high covariation at the phenotypic level appears to be shaped by high covariation at the genetic level (Lahey et al., 2011). According to this proposed genetic architecture, common sources of genetic variability drive comorbidity between symptomatically related disorders within syndrome spectra. However, the precise biological mechanisms though which genes predispose risk for broad syndrome spectra remain unresolved. Here, we propose that connectivity circuits may be systems-level units that underlie the observed clustering of symptoms. According to our model, genetic liability to psychopathology disrupts the function of brain connectivity circuits, producing deficits in core domains of cognition that manifest as transdiagnostic symptom clusters (Figures 1 and 2). As one example, executive dysfunction spans diagnostic taxons; a genetic variant perturbing frontoparietal connectivity would, almost necessarily, increase susceptibility to multiple disorders, because the resulting deficits in executive function are not disorder specific. While it would still be a simplification to assume that genetic variants have an impact on only one such circuit (Meyer-Lindenberg and Weinberger, 2006), this model proposes that pleiotropic effects on symptom clusters are consistently mediated by circuits associated with these clusters across diagnostic categories.

Our proposal is grounded in the assumption that genetic factors significantly contribute to psychopathology-linked patterns of altered connectivity. If this assumption is valid, measures of functional connectivity should show significant heritability. The evidence supports this. For example, the unaffected siblings of patients with schizophrenia show alterations in frontoparietal connectivity that mirror changes seen in illness (Woodward et al., 2009; Rasetti et al., 2011). Further, a recent linkage analysis in 29 extended pedigrees confirms the heritability of resting-state DMN connectivity (Glahn et al., 2010). These findings confirm that genetic factors shape connectivity in networks linked to symptom domains, and imply that connectivity changes observed in mental disorders reflect a cause, rather than a consequence, of being ill. Of course, this concept can be easily extended to other causal factors associated with mental illness, in particular, environmental or epigenetic effects.

Genetic imaging studies support the idea that heritable differences in brain connectivity contribute to the dimensionality of mental illness. Here, we unpack this concept by detailing connectivity findings for several well-characterized pleiotropic genetic variants.

COMT

A functional coding variant (rs4680; val158met) within the gene encoding the dopamine catabolic enzyme catechol-o-methyltransferase (COMT) has been shown to exert pleiotropic effects on cognition, mood, and related disorders. The 158val allele, linked to increased enzyme stability and lower dopamine levels in brain, has modest associations to psychotic disorders and cognitive performance (Allen et al., 2008; Goldman et al., 2009), and strong associations to prefrontal function during cognitive tasks (Mier et al., 2010). The 158met allele, linked to decreased enzyme stability and higher dopamine levels in brain, has modest associations to substance abuse, mood disorders, and anxiety disorders and strong associations to corticolimbic function during affective tasks (Stein et al., 2005; Pooley et al., 2007; Lohoff et al., 2008; Kolassa et al., 2010; Mier et al., 2010; Åberg et al., 2011). Consistent with 158val associations to executive cognition symptoms in illness, this allele is linked to anomalous frontoparietal connectivity during working memory (Tan et al., 2007, 2012). In accord with 158met associations to symptoms of negative affect in substance abuse, mood disorders, and anxiety disorders, this allele predicts exaggerated amygdala-VMPFC connectivity during negative emotional arousal (Drabant et al., 2006).

ZNF804A

A series of genome-wide association studies in schizophrenia and bipolar disorder provide evidence that ZNF804A variation predisposes risk for a broad psychosis phenotype (O'Donovan et al., 2008; Riley et al., 2010; Williams et al., 2011). The variant showing most consistent evidence of association, an intron 2 SNP (rs1344706), has also been linked to schizotypal traits and impoverished social cognition (Balog et al., 2011; Yasuda

et al., 2011). Imaging genetic studies imply that ZNF804A associations to these disorder-spanning symptoms may reflect genetically influenced alterations in network function. ZNF804A risk allele carriers demonstrate aberrant DLPFC-TPJ coupling during mental state inference ("theory of mind"), which may contribute to transdiagnostic symptoms of social dysfunction (Walter et al., 2011). In addition, risk carriers show aberrant DLPFC-VLPFC and DLPFC-hippocampal connectivity during working memory, a heritable connectivity phenotype that is seen in patients with schizophrenia and their siblings (Esslinger et al., 2011; Rasetti et al., 2011), and a likely human homolog of altered hippocampal-prefrontal synchrony reported in an animal model of psychosis (Sigurdsson et al., 2010).

MAOA and 5HTT

Genes encoding the monoamine catabolic enzyme monoamine oxidase A (MAOA) and the serotonin transporter (SLC6A4; 5HTT) both have notable histories of association to psychiatric illness. The most commonly studied risk variants in both of these genes (upstream tandem repeat polymorphisms) are both associated with reduced serotonin clearance in the synapse leading to elevated serotonergic tone, particularly during early development (Holmes and Hariri, 2003; Buckholtz and Meyer-Lindenberg, 2008). MAOA genetic variation is most notably associated with risk for antisocial behavior and impulsive-aggressive traits, especially in combination with early life maltreatment. By contrast, 5HTT genetic variation is most prominently associated with risk for mood and anxiety disorders and with neuroticism traits, particularly in combination with high levels of life stress.

However, both genes show evidence of pleieotropy: MAOA predisposes risk for MDD in addition to antisociality (Fan et al., 2010; Zhang et al., 2010; Lung et al., 2011; Nikulina et al., 2012), and 5HTT predisposes risk for antisocial behavior in addition to depression (Beitchman et al., 2006; Haberstick et al., 2006; Sakai et al., 2006, 2007). Critically, both impact a corticolimbic circuit for emotional arousal and regulation (amygdala-cingulate-VMPFC) that is commonly dysregulated in both MDD and antisocial behavior. In other words, risk variants in two separate genes disrupt connectivity in the same brain network, increasing susceptibility to a broad domain of psychopathology that is chiefly characterized by symptoms of heightened emotional reactivity and poor affect regulation. Such symptoms are common to both MDD and antisocial personality disorder. This is consistent with our proposal that connectivity circuits convey symptom-specific/disease-general genetic risk for mental illness.

CNTNAP2

Interest in the neurexin superfamily gene CNTNAP2 (encoding the contactin-associated protein-like 2) was initially piqued by a series of cytogenic, linkage, association, and gene expression studies in autism (Alarcón et al., 2008; Arking et al., 2008). More recent studies show strong evidence for pleiotropy, with a suggestive pattern of transdiagnostic associations to schizophrenia, BD, and social anxiety (Wang et al., 2010a; O'Dushlaine et al., 2011; Stein et al., 2011). Risk allele carriers show connectivity changes within the DMN (PCC-MPFC), and between mPFC and task-positive nodes such as DLPFC (Scott-Van Zeeland et al., 2010). Thus, it is possible that CNTNAP2 variation produces disease-general social cognitive symptoms by influencing DMN network function. Though intriguing, more work is necessary to characterize the implications of CNTNAP2-linked DMN dysregulation for social cognitive dysfunction across disorders.

DRD2

Allelic variants in and near the gene encoding the dopamine D2 receptor (DRD2) show significant pleiotropic effects, with associations to schizophrenia, ADHD, substance abuse, and antisocial behavior (Xu et al., 2004; Nyman et al., 2007; Allen et al., 2008; Kollins et al., 2008; Colzato et al., 2010; Lu et al., 2010). The linkage between DRD2 variation and these seemingly diverse phenotypes may be driven by an effect on frontostriatal circuitry for flexible, value-based action selection (Cools, 2008; Balleine and O'Doherty, 2010). Consistent with this idea, DRD2 susceptibility allele carriers have atypical frontostriatal connectivity during tasks of cognitive flexibility and reward learning (Cohen et al., 2007; Krugel et al., 2009; Stelzel et al., 2010). Genetically determined differences in dopamine receptor function may therefore moderate the expression of dimensional symptoms pertaining to reward motivation and cognitive control, such as impulsivity, compulsivity, and risk taking (Limosin et al., 2003; Dalley et al., 2008; Colzato et al., 2010; Buckholtz et al., 2010a; 2010b; Laughlin et al., 2011).

Phenotypic Heterogeneity: Polygenic Risk and Gene-by-Environment Interactions

As we mention in a preceding section, genetic studies in mental illness increasingly support a polygenic model of inheritance. Many small-effect alleles and possibly several rare, but highly penetrant variants combine to produce illness (International Schizophrenia Consortium et al., 2009; Rucker and McGuffin, 2010; Frank et al., 2012; Gejman et al., 2011). This has two important implications for thinking about neurobiological mechanisms that mediate risk for mental illness. First, though we treat specific genetic risk factors here as though they are individual causal entities, they are far from deterministic in isolation. Accordingly, effect sizes for single genetic variants on psychiatric phenotypes are typically quite small. Second, polygenicity implies a continuous model of liability. Variability in the specific collection of alleles harbored in an individual genome produces quantitative individual differences in multiple domains of biological function. Consequently, an individual's aggregate genetic profile will determine where they fall on multiple distributions of cognitive functioning. The extremes of these genetically influenced distributions are associated with impairment and dysfunction, manifesting clinically as symptoms. We argue here that circuit-level connectivity is a quantitative trait that links genetic variability and symptom variability (Figure 4). Each individual's polygenic profile will affect each of the circuits we've outlined here to a varying degree. Across individual genomes, patterns of genetic covariance would lead to patterns of covariance in connectivity producing patterns of symptom covariance (i.e., comorbidity). In other words, the latent structure of psychopathology may reflect, in part, a genetically determined latent structure of brain connectivity.

Though we have focused on genetic risk in this review, environmental factors are clearly critical in determining susceptibility to psychopathology. Importantly, data continues to accrue that environments affect connectivity as well: chronic psychosocial

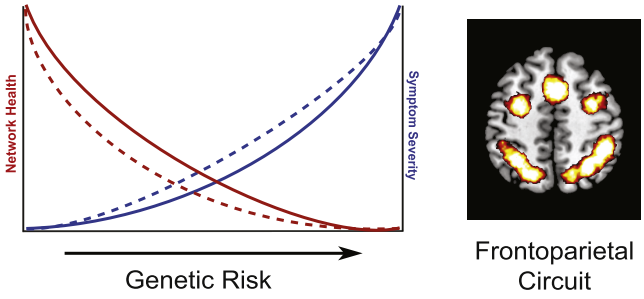

Figure 4. Polygenic Liability to Psychopathology Produces Continuous Variation in Network Functioning and Psychiatric Symptoms

We propose here that individual variation in connectivity and symptom expression are determined by multiple small-effect alleles. Across the population, continuous variability in the aggregate burden of deleterious alleles harbored in each individual genome (polygenic liability) produces quantitative differences in the function of a given brain network, and in the expression of network-specific symptoms. In the case of the frontoparietal network depicted here, higher polygenic liability would be associated with atypical connectivity and relatively greater expression of executive symptoms such as poor working memory and distractibility. Dashed lines depict the greater penetrance of genetic liability on connectivity and symptoms in the presence of environmental risk factors, such as childhood maltreatment or chronic stress.

stress disrupts frontoparietal circuits for attentional control (Liston et al., 2009), social context factors such as urbanicity and low socioeconomic status impinge upon corticolimbic and frontostriatal circuits for affect regulation and behavioral flexibility (Gianaros et al., 2011; Lederbogen et al., 2011), and prenatal risk factors such as intrauterine cocaine exposure adversely affect DMN connectivity(Li et al., 2011). Individual environments may act to modify the penetrance of genetic risk factors (Hicks et al., 2009) by magnifying the impact of genetic variability on connectivity circuits via epigenetic processes. Alternatively, genetic factors may compromise functional integration across a number of networks, making those systems more vulnerable to the effects of adverse environments (Buckholtz and Meyer-Lindenberg, 2008). Whatever the specific mechanism, latent risk for broad spectra of psychopathology and individual environmental exposures almost certainly interact to affect connectivity, focusing symptom expression toward more specific endpoints (Lahey et al., 2011). However, the available body of data on environment and connectivity is not extensive. For example, while it is well known that environmental risk factors such as childhood maltreatment can have enduring impact on regional structure and function, for example in cingulate and amygdala (Dannlowski et al., 2012), much less is known about the effects of such stressors on connectivity circuit features. Such data, especially if they show different effects across the life span, could add another layer of explanatory power to the proposal to decompose psychopathology across circuit profiles linked to causal factors and symptom clusters.

Limitations and Suggestions

There are several limitations that warrant consideration. First, in marshaling empirical evidence to support our model, we chose to focus on specific network components where dysfunction is clearly evident across disorders (e.g., DLPFC-amygdala; MPFC-ventral striatum). However, a key feature of functional integration is its multinodal nature. By considering the coupling of two network nodes in isolation, we may overlook important multidimensional alterations that are present in the larger network context. Graph analytic approaches derived from complex network analysis may be especially valuable for determining the holistic patterns of network dysfunction that map best onto symptom domains.

Second, we do not explicitly take task-specific effects on connectivity into account, and have instead opted to generalize from the body of available connectivity data. In terms of the relationship to latent cognitive processes, it is not clear how frontoparietal connectivity during an n-back working memory task is meaningfully different from frontoparietal connectivity during a Sternberg working memory task (to use one example). Nor is it evident how frontoparietal connectivity during either of those tasks differs from frontoparietal connectivity observed during a cued attention task. This issue is related to larger problem within cognitive neuroscience: the lack of a valid taxonomy of cognitive processes (Poldrack et al., 2011). We do not have a consensus understanding of the discrete components that comprise cognition, their relationships to one another, or how they map onto specific experimental tasks (Badre, 2011). Experimental paradigms frequently index multiple cognitive factors, and performance on different tasks that purport to measure the same cognitive process (e.g., working memory) often correlate weakly, reflecting the ambiguity of even well-studied cognitive constructs (Kane et al., 2007; Poldrack et al., 2011). These limitations lower our level of precision in linking specific cognitive processes to clinical symptoms, risk factors, and brain connectivity networks. As the field moves toward an empirically derived classification of psychopathology, one based on quantitative measures of behavior and neurobiology, illuminating the latent structure of cognition will be key. Especially promising approaches include the incorporation of cognitive factor analysis in task-based fMRI data analysis (Badre and Wagner, 2004), online cognitive ontologies that enable classifier-based and meta-analytic parsing of cognitive constructs (Bilder et al., 2009; Poldrack et al., 2011), and large-scale syntheses of fMRI data that permit decoding of brain activity patterns for these constructs via similar methods (Yarkoni et al., 2011).

Third, we note that while alterations in connectivity can produce psychological symptoms in the absence of regional pathology, the converse may not be strictly true. Because dynamic reorganization is a key property of functional brain networks, regional deficits may reconfigure the networks in which a region is embedded. For example, interfering with the function of one DMN node via transcranial magnetic stimulation leads to a reorganization of DMN architecture (Eldaief et al., 2011). This brings a central tenet of our model into relief. Here, we outline the importance of circuits for conveying category-spanning genetic risk for psychopathology. We suggest that distinct genetic risk factors for the same transdiagnostic symptom domain impact a common circuit. However, they may do so via different proximal means; e.g., by preferentially affecting processing within partially or non-overlapping network

nodes due to differences in region-specific expression. Despite such proximal differences, the net effect of these variants on symptom expression will be similar because of their common influence on network functioning.

Fourth, our model largely considers specific brain circuits as relatively independent entities that map selectively onto circumscribed symptom domains. The reality is clearly more complex. Impulsivity provides a potentially instructive example. Impulsive symptoms contribute to impairment and distress in many disorders, including schizophrenia, bipolar mania, ADHD, antisocial personality disorder, and substance dependence (Moeller et al., 2001; Swann et al., 2002). We have "assigned" impulsive symptoms to the corticostriatal network in our model because there is a large body of work linking impulsivity to corticostriatal information processing (Winstanley et al., 2006; Dalley et al., 2008; Buckholtz et al., 2010a, 2010b; Peters and Büchel, 2011). However, impulsivity is a heterogeneous construct with dissociable cognitive components. Deficits in response inhibition, performance monitoring, and goal-directed attention (indexed by go/no-go, stop-signal, and continuous performance tasks) may contribute to "impulsive action." By contrast, deficits in value-based decision-making (indexed by delay discounting tasks) are linked to "impulsive choice." These facets of impulsivity have some unique relationships to psychopathology and may map onto overlapping, or interacting, connectivity circuits (Christakou et al., 2011; Conrod et al., 2012). Though not considered here, interactions between cognitive domains, and the networks that support them, are undeniably important for determining how psychiatric symptoms such as impulsivity are expressed. Heritable alterations in between-network connectivity have been reported in psychosis (Whitfield-Gabrieli et al., 2009; Repovs et al., 2011; Meda et al., 2012), but data in other symptom domains is more limited. Moving forward, it is useful to consider the role that aberrant connectivity between networks may play in mediating genetic liability to psychopathology.

Fifth, with a few exceptions, we don't explicitly discuss the directionality of connectivity differences in patients or risk variant carriers. There is directional heterogeneity in the literature, even between two studies using the same task in the same disorder. However, compelling directional inferences are difficult to make from functional connectivity studies, and are model dependent in effective connectivity studies. Moreover, given the artificiality of DSM-based classification, directional comparisons between patient studies that use the same categorical diagnosis may be confounded by biological heterogeneity. One approach that addresses this issue is symptom-specific association (Chabernaud et al., 2011; Shannon et al., 2011); we hope that more patient studies using biological measures will begin to adopt this approach.

Finally, development of the ideas outlined here will need to take lifespan issues and plasticity into account. There is clear evidence that connectivity patterns and plasticity vary across the life cycle, that both experience-dependent plasticity and environmental contributions may have widely different effects depending on the time of exposure, and that critical periods, such as puberty, exist whose specific in terms of connectivity need to be elucidated fully.

Conclusions

Synthesizing available genetic, neuroimaging and clinical data, we propose a dimensional "common symptom, common circuit" model of psychopathology. We hope that our model will be a useful heuristic that will aid the field as it moves toward a neuroscience-based empirical classification of mental illness. A key tenet of this model is that risk factors for mental illness produce alterations in brain circuit function that induce susceptibility to psychopathology in a manner that is cognitive and symptom domain-specific, but disorder-general. We argue that the linkage between common symptom variance and common genetic variance is a function of the effect of that shared genetic liability on brain networks underlying symptom-relevant cognitive domains. This model would predict that variance in the function of specific connectivity circuits would be represented as distinct higher order factors that link genetic variance and circuit-appropriate symptom variance, and could be tested by confirmatory factor analyses in large, epidemiologically valid twin designs that incorporate dimensional symptom ratings and connectivity measures. We believe that the integration of brain connectivity into genetically informative and phenotypically rigorous experimental designs represents a crucial step forward toward an empirically grounded quantitative nosology of mental illness.

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